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Ser-660 phosphorylation of protein kinase C beta II (PKC β II) by mammalian target of rapamycin complex 2 (mTORC2) regulates high glucose (HG) induced mesangial cell hypertrophy

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Protein kinase C beta II (PKC β II) has been implicated in diabetic nephropathy (DN). Mesangial cell (MC) hypertrophy is a pathologic feature of DN. PKC β II undergoes phosphorylation at the hydrophobic motif site Ser-660 for its activity. We have shown that mTOR complex 1 (C1) regulates MC hypertrophy. How activation of PKC β II by Ser-660 phosphorylation fits into mTOR signaling to control MC hypertrophy is not known. HG significantly increased phosphorylation of PKC β II at Ser-660 in a PI 3 kinase dependent manner. siRNAs against PKC β II, dominant negative PKC β II and non-phosphorylatable mutant of PKC β II, PKC β IIS660A, blocked mTORC1 activity due to lack of PRAS40 phosphorylation, resulting in significant inhibition of HG induced MC protein synthesis and hypertrophy. Also, PKC β IIS660A attenuated phosphorylation of Akt at Ser-473, a putative mTOR complex 2 (C2) site. Specific inhibition of mTORC2 by shRNAs against rictor or Sin1, two exclusive and required components for its activity, suppressed HG induced phosphorylation of PKC β II Ser-660 and Akt Ser-473, resulting in attenuation of mTORC1 activity leading to inhibition of MC hypertrophy. Constitutively active (CA) Akt or CA mTORC1 reversed shRictor or shSin1 mediated inhibition of HG induced MC hypertrophy. Furthermore, CA PKC β II reversed the shRictor or shSin1 induced inhibition of HG stimulated Akt Ser-473 phosphorylation and MC hypertrophy. Finally, we show increased phosphorylation of PKC β II Ser660, PRAS40 and Akt Ser-473 in association with activation of mTORC1 in renal cortices of OVE26 mice with type-1 diabetes. These results provide the first evidence that HG induced activation of mTORC2 phosphorylates and activates PKC β II to increase the phosphorylation of Akt at Ser-473 to finally activate mTORC1 to induce MC hypertrophy. Thus, we uncover a specific role of mTORC2 for Akt/mTORC1 activation via PKC β II Ser-660 phosphorylation.

Biography

Falguni Das has received his PhD from University of Calcutta, India. He has joined the Department of Medicine's Division of Nephrology as a Post doctoral fellow at University of Texas Health Science Center at San Antonio. He has worked extensively in areas of kidney physiology, signal transduction, gene regulation and the fundamental pathogenic mechanism of injury to kidney. He has produced several exciting findings which have been published in highly reputed journals. He has received several prestigious awards from his own institutes and also like New York Academy of Sciences.

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